Kidney International, Vol. 57, Suppl. 75 (2000), pp. S-38–S-43

Dietary therapy in uremia: The impact on nutrition and progressive renal failure

William E. Mitch

Renal Division, Emory University School of Medicine, Atlanta, Georgia, USA

Dietary therapy in uremia: The impact on nutrition and progressive renal failure.

Background. In rats with experimental chronic renal failure (CRF), low-protein diets protect against histologic damage and improve mortality. In CRF patients, low-protein diets ameliorate uremic symptoms and certain CRF complications. Fortunately, low-protein diets are nutritionally sound in CRF patients because they activate compensatory mechanisms that conserve protein with a low-protein diet. These results do not determine if dietary protein restriction can slow the rate of progression of CRF or the time to dialysis.

Methods. Reports evaluating low-protein diets and changes in nutritional status and/or progression of CRF are analyzed for efficacy. The MDRD Study is reviewed in depth.

Results. When dietary compliance was achieved, the nutritional status was unimpaired and progression was slowed. Studies with limited dietary compliance failed to find any beneficial effect on progression. Problems in study design suggest caution before accepting the initial MDRD Study conclusion that dietary restriction does not slow progression. Subsequent analyses of MDRD results indicate that protein restriction can slow progression of CRF.

Conclusion. Evidence that dietary protein spontaneously decreases in progressively uremic patients should not be construed as an argument against the use of dietary therapy. Rather, it is a persuasive argument to restrict dietary protein intake in order to minimize CRF complications while preserving nutritional status. In patients with uremia or progression despite other measures, dietary therapy should be started along with monitoring for dietary compliance and nutritional adequacy.

For more than a century, it has been known that a protein-restricted diet can ameliorate many uremic symptoms and during the past 30 years, dietary manipulation was shown to prevent or treat some of the complications of chronic renal failure (CRF) including renal osteodystrophy, hypertension, electrolyte disturbances and metabolic acidosis [1]. These improvements occur because a low-protein diet invariably restricts the intake of phosphates, sodium, and acid that cause these complications. Less impressive evidence suggests that low-protein diets can slow progression of renal insufficiency.

Key words: low-protein diets, progression, kidney, nutrition, diet

More than 70 years ago, it was shown that a diet rich in protein exerted adverse effects on the kidney function of rats [2]. In the 1930s, Chanutin and Ludewig studied rats after subtotal nephrectomy and found that feeding a high content of varying types of protein led to more severe hypertension, more interstitial damage and a higher mortality [3]. In 1942, Farr and Smadel reported the same results in rats with experimental serum nephritis [4]. More recently, this theme was extended by showing that a low-protein diet prevents the adaptive increase in glomerular capillary pressure occuring in CRF and it was proposed that this is the mechanism leading to progressive glomerular sclerosis [5]. Glomerular capillary hypertension was later linked to activation of the renin-angiotensin system, another consequence of excess dietary protein [6, 7]: angiotensin causes glomerular efferent arteriolar constriction, and hence glomerular hypertension, while aldosterone has nephrotoxic properties. Another, perhaps allied theory is that proteinuria initiates mechanisms that produce progressive interstitial nephritis [8]. Certainly, higher levels of proteinuria are associated with faster rates of loss of renal function [9], and a low-protein diet reduces the degree of proteinuria, but whether this is the mechanism for the protective effect of a low-protein diet is unclear [10]. A third mechanism involves hypertension-induced kidney damage. A low-protein diet does restrict sodium intake, but it is difficult to link a lower sodium intake to changes in the degree of damage to the kidney. Thus, there is abundant experimental evidence and even proposed mechanisms to explain why too much dietary protein is associated with progressive kidney damage. There also are caveats: in a careful pair-feeding protocol, it was concluded that the amount of food and/or calories eaten is associated with kidney damage in rats; moreover, in other species with CRF (e.g., baboons) a high-protein diet does not accelerate renal insufficiency [11, 12].

In evaluating the effects of any therapy, including dietary manipulation, on the course of progressive renal insufficiency, it is important to remember two facts. The first is that the loss of renal function in individual patients

is not chaotic but rather, usually predictable. This is based on our finding in 1976 that the rate of loss of renal function in individual patients could be determined by plotting the reciprocal of serum creatinine (S_{Cr}) against time [13]. This means that creatinine clearance and glomerular filtration rate (GFR) are being lost in a predictable fashion [14]. Even though there is controversy about the use of S_{Cr} in gauging the loss of renal function in patients being treated with low-protein diets, if there is long-term (e.g., months to years) stability of S_{Cr}, there must be stability of creatinine clearance or GFR [2, 14]. The second finding is that each patient has his/her own rate of loss of residual renal function and hence, there is no rate that can be said to be characteristic of a specific kidney disease. For example, the rate of loss of renal function in diabetic patients can vary more than 40-fold [15].

DIETARY MANIPULATION IN PATIENTS WITH PROGRESSIVE RENAL FAILURE

When evaluating studies of dietary therapy and their impact on progressive renal failure, three questions should be considered: (1) does the diet cause malnutrition; (2) has dietary adequacy been monitored and compliance achieved; and (3) has restricting the diet changed the rate of loss of renal function? These questions can be evaluated using the following considerations.

Do low-protein diets cause malnutrition?

The finding that dialysis patients often have low levels of serum proteins and evidence of malnutrition has led some to suggest that low-protein diets should be used cautiously or avoided and that dialysis of CRF patients should be initiated early [16, 17]. It is true that if CRF patients are not instructed in the composition, and how to accomplish dietary goals, there may well be a spontaneous decrease in protein intake and deterioration of some nutritional indices [16]. Another worrisome report is the association between hypoalbuminemia and increased mortality in hemodialysis patients [18], but hypoalbuminemia in these patients can be linked as much to evidence of inflammation as it is to dietary inadequacy [19]. In fact, CRF patients treated with low-protein diets were found to have an increase in serum protein concentrations at the initiation of dietary therapy [20]. A low-protein diet is also associated with improved survival of CRF patients who subsequently began dialysis [21]. Finally, there is abundant evidence that with proper implementation, a low-protein diet yields neutral nitrogen balance and maintenance of normal serum proteins and anthropometric indices during long-term therapy [20, 22, 23]. Regarding nutritional adequacy, three diets have been used to slow the progression of CRF: a low-protein diet providing 0.6 g protein/kg ideal body weight/day; a very low-protein diet (VLPD) containing ~0.3 g protein/kg/day of predominantly vegetable protein supplemented with a mixture of essential amino acids (EAA); or the same VLPD diet supplemented with a mixture of EAA and the nitrogen-free analogs of amino acids (ketoacids). The design of these diets requires attention to energy intake, vitamin and mineral requirements, etc. [24], but with proper guidance, each yields neutral nitrogen balance and is nutritionally sound during long-term therapy. Kopple and Coburn demonstrated that the dietary protein requirement of patients with uncomplicated CRF is ~0.6 g protein/kg/day, the same as that for normal adults [25] while others showed that supplemented VLPD diets produce nitrogen balance in CRF patients [22, 23]. Regarding long-term results, the Modification of Diet in Renal Disease Trial (MDRD) showed that these diets are not associated with biologically important changes in body weight, mid-arm muscle circumference or serum proteins [26]. Importantly, no patient had to withdraw from the MDRD trial because of impaired nutritional status. Nitrogen balance is achieved with these low-protein diets because CRF patients like normal adults, activate adaptive metabolic responses: they reduce the oxidation of EAA to ensure a sufficient EAA supply and they decrease postprandial protein degradation (at least as long as there is no catabolic stimulus such as metabolic acidosis) [22, 27].

Monitoring dietary adequacy and compliance

Success with dietary therapy requires periodic assessment of dietary compliance and nutritional status. Fortunately, there is a simple method for estimating the protein intake of CRF patients [28]. The method is based on urea nitrogen production because nitrogen derived from dietary or endogenous protein is converted principally to urea so the sum of urea excreted plus accumulated (i.e., the urea nitrogen appearance rate) closely parallels protein intake. In contrast, the nitrogen in urinary compounds such as creatinine, uric acid, ammonia, etc. and feces (i.e., nonurea nitrogen excretion) does not vary significantly with protein intake: it averages 0.031 g nitrogen/kilogram ideal body weight/day [28]. To monitor compliance, the 24 hour urea nitrogen excretion is added to the estimated value of nonurea nitrogen excretion ($0.031 \times$ body weight). The sum is equal to nitrogen intake if the patient is in steady-state and weight and serum urea nitrogen are constant. This method makes it possible to evaluate compliance and hence, the efficacy of a diet on changing progression.

Nutritional status is monitored by serial measurements of anthropometrics, serum albumin, and transferrin. The assistance of a skilled dietician is required for successful monitoring of patients prescribed low-protein diets [2].

PROTEIN RESTRICTION AND PROGRESSION OF RENAL INSUFFICIENCY

Unsupplemented low-protein diets and progression

In one of the earliest trials, Maschio et al evaluated three groups of patients: Groups I and II had initial S_{Cr} values of 1.6–2.7 and 2.9–5.4 mg/dL, respectively, and were prescribed a diet containing 0.6 g/kg of predominantly high-quality protein, 40 kcal/kg energy intake, ~650 mg of phosphorus and 1.0–1.5 g of calcium; Group III, the control group (initial S_{Cr}, 1.6–4.7 mg/dL), consumed an unrestricted diet [29]. Although dietary compliance was not rigorously evaluated, the loss of renal function in Groups I and II was far slower than in Group III. Subsequently, this group noted similar results after an average of 54 months in a larger group of patients [30]. Individuals who began a low-protein diet early had a more favorable course and patients with interstitial nephritis fared better than those with chronic glomerulonephritis or polycystic kidney disease. The initial S_{Cr}, level of proteinuria and blood pressure were independent risk factors for progression.

Rosman et al reported the results of a prospective, randomized trial involving 149 patients followed for an average of 24 months after being assigned to a low-protein or a control diet [31]. From the reported urea excretion values, the difference in protein intake between the protein-restricted and control subjects averaged 18 g/day [28] and even with this small change, there was significant slowing of progression (3–5-fold slower) with the low-protein diet. Four years later, they reported on 153 of 248 patients treated similarly [32]. There still was a detectable, albeit less significant, benefit of a low-protein diet in slowing progression, but now the benefit was in patients with more advanced renal insufficiency, with glomerulonephritis and in men more than women. To avoid the problems of using S_{Cr}, Ihle et al conducted an 18-month prospective, randomized comparison of a low-protein and an unrestricted diet on changes in GFR (plasma disappearance of tracer) [33]. Eight of the initial 72 patients with advanced CRF were excluded, as 3 withdrew voluntarily and 5 were excluded for noncompliance with the diet or were taking medications that interfered with the analysis. End-stage renal disease (ESRD) developed in 9 of 33 patients (27%) who were given an unrestricted diet, compared to only 2 of 31 (6%) of those compliant with the protein-restricted diet ($P < 0.05$). The average GFR decreased 60% in the control group from 15 to 6 mL/min ($P < 0.01$) but minimally (14–12 mL/min, P = NS) in the low-protein diet group. The average protein intake calculated from urea excretion was ~0.7 in the low protein group and ~0.95 g/kg/day in the unrestricted group [2, 28].

In contrast to these studies, there are results of trials in which there was little or no change in the intake of protein [2, 34–36]. Predictably, there also was no benefit of the low-protein regimens on progression of CRF.

There also is evidence that low-protein diets can slow progression of diabetic nephropathy without compromising nutritional status. Walker et al examined the GFR of 19 patients with type I insulin-dependent diabetes mellitus (IDDM), proteinuria and progressive CRF while they consumed an unrestricted diet (1.13 g protein/kg/day) [37]. When the patients were switched to a diet providing 0.67 g protein/kg/day, the loss of GFR slowed significantly (i.e., 0.61–0.14 mL/min/month) as did the rise in albuminuria. These benefits were statistically significant even after adjustment for differences in blood pressure, energy intake and glycosylated hemoglobin levels. Raal et al compared diets of 0.8 or ≥1.6 g protein/kg/day in a 6-month study of 32 type I IDDM patients with proteinuria and GFR of 50–66 mL/min/1.73 m^2 [38]. With the low-protein diet, there was no further decline in GFR and proteinuria significantly decreased but with the high protein diet, patients lost GFR and proteinuria increased even in this short-term study. Zeller et al reported results of a randomized, prospective, controlled trial of Type I diabetic patients with nephropathy treated for an average of 35 months [39]. Fifteen patients were assigned to a control diet of 1.0 while 20 patients were assigned to a diet with 0.6 g protein/kg/day. Blood pressure and the degree of glycemic control were comparable in the groups. The rate of decline in GFR (renal clearance of ^{125}I-iothalamate) was 4-fold slower with the low-protein diet (−3.1 versus −12.1 mL/yr, respectively; $P < 0.02$). Although the mean arterial pressure was ~3 mm Hg lower in the low protein group ($P < 0.05$), the authors attributed the slowing of progression to the low-protein diet since this small change and the similarities in glycemic control and frequency of visits to the doctor could not account for the benefit.

Ketoacid-supplemented low-protein diets and progression

A VLPD diet supplemented with ketoacids also seems to slow progression of CRF. Barsotti et al treated 27 compliant, CRF patients who had a linear decrease in their creatinine clearances using a regimen containing about 0.2 g protein/kg/day plus a supplement of the calcium salts of ketoacids [40]. The loss of creatinine clearance was interrupted after beginning dietary therapy. Using another regimen of a VLPD plus ketoacids given as salts of the basic amino acids, ornithine and lysine over an average of 20 months, we found that the loss of renal function in 10 of 17 patients with well-defined rates of progression (as assessed by changes in the reciprocal of S_{Cr}) was halted [41]. Walser et al compared an EAA-based to a ketoacid-based, VLPD regimen in 12 patients with advanced CRF using a cross-over study design (i.e., KA then EAA and vice versa) [42]. The ketoacid regi-

men appeared to slow progression to a greater degree than the EAA regimen. Although the number of patients is small, it is important to emphasize that progression can be delayed even in patients with advanced CRF.

The Modification of Diet in Renal Disease Study

The NIH-sponsored MDRD Study contained the largest number of patients participating in a trial of the influence of low-protein diets on progression of CRF [43]. This multicenter, randomized, prospective trial was designed to evaluate whether two levels of blood pressure (usual mean arterial pressure [MAP] = 107 mm Hg or ~140/90 versus low MAP = 92 mm Hg or ~125/75) and different levels of protein intake would slow the progression of CRF; diabetics were excluded. Hypertension was treated with angiotensin-converting enzyme inhibitors (ACEi) or other drugs in an unregulated fashion. In Study A, 585 patients with GFRs between 25 and 55 mL/min were randomly assigned to their usual or a low-protein diet (1.3 versus 0.58 g protein/kg/day); in Study B, 255 patients with GFRs between 13 and 24 mL/min were randomly assigned to a low or a very low-protein diet (0.58 versus 0.28 g protein/kg/day). In Study B, the VLPD diet was supplemented with ketoacids but no control diet was included for comparison with the low protein regimens. Protein intake assessed [28] and GFR (renal clearance of ^{125}I-iothalamate) was measured every 4 months over an average follow-up of 2.2 years. Compliance with the prescribed protein intake was quite good (Study A; 1.11 ± 0.19 versus 0.73 ± 0.15; Study B, 0.69 ± 0.12 versus 0.46 ± 0.15 g protein/kg/day, [mean ± SD at 2 years follow-up]). During the first four months, renal function declined more rapidly in Study A patients assigned to the low protein and low blood pressure groups ($P = 0.004$ and < 0.01, respectively). Thereafter, the rate of decline in GFR was 28% slower in the low protein ($P = 0.009$) and 29% slower in the low blood pressure group ($P = 0.006$). However, when the results were analyzed from the initial to the final GFR values and compliance was ignored in an intention-to-treat analysis, the projected decline in GFR did not differ significantly between diet or blood pressure groups. In the analysis of patients with more advanced CRF (Study B), the loss of GFR was 19% slower in the very low protein compared to the low protein group ($P = 0.065$) but the cumulative incidence of end-stage renal disease or death was not different. Notably, the lower blood pressure groups also did not exhibit slowing of progression in either Study A or Study B, with the exception that progression was significantly slower when there was > 1 g proteinuria/day. The authors concluded that with moderate CRF (Study A), the slower decline in renal function that began 4 months after beginning the low-protein diet suggests a small benefit of protein restriction. In Study B, they concluded that the effects of the two diets were similar but there was no control group to determine if dietary protein restriction was beneficial in patients with more advanced renal insufficiency.

These results might seem to strike the death knell for the proposal that dietary protein restriction will slow progressive renal damage in CRF patients as it does in rats with CRF. However, such an interpretation is complicated by several factors. Firstly, the sample size was based on the assumption that GFR would decline ~6 mL/min/yr in patients eating an unrestricted diet and maintaining their usual blood pressure. Overall, however, progression was ~30% slower than expected, dampening the power to detect a benefit of the diet. This problem was compounded by two additional factors: (1) patients enrolled in the MDRD Study did not have to exhibit evidence of progressive renal insufficiency and approximately 15% of the Study A control group had no evidence of loss of GFR making it impossible to demonstrate slowing of progression. (2) A disproportionate number of patients (~20%) had polycystic kidney disease, and progression in these patients appeared to be unaffected by dietary means or aggressive treatment of hypertension. Inclusion of these patients could obscure a benefit of the diet on progression in patients with other kidney diseases. Secondly, the use of ACEi could make the benefit of a low-protein diet more difficult to detect. Another complication was in the mixture of ketoacids in the MDRD Study since it differed from the mixture that was reported to slow progression in other studies [41, 42, 44]. Thirdly, the initial rapid GFR decline in Study A patients assigned to the low protein and low blood pressure groups was unexpected and could have obscured a slowing of progression subsequently. This raises the issue of the short (2.2 years) duration of the study; in an evaluation of another metabolic intervention on kidney function (the DCCT Trial [45]), strict glycemic control exerted no suppressive effect for 4 years but then a benefit on proteinuria was obvious. Finally, there was no control diet in Study B, so the results neither support nor refute a benefit of dietary protein restriction in patients with advanced renal insufficiency.

These factors make it unwise to conclude that the MDRD Study proves that dietary manipulation does not slow progression of CRF. As discussed, this type of conclusion does not address the central hypothesis that eating a low-protein diet can slow the progression of CRF. In fact, when MDRD results were analyzed based on the amount of protein actually consumed, a benefit of dietary protein restriction in Study B patients was obvious: each 0.2 g/kg/d reduction in protein intake was associated with a 29% slower rate of loss of GFR and a 51% prolongation in the time to dialysis ($P < 0.01$) [46, 47]. Although no independent influence of the ketoacid regimen was detected, this conclusion might differ if another ketoacid mixture were used in the MDRD Study [44]. Regarding

the ability to make generalized conclusions, there also are the problems discussed about the reliability of the analysis: the meta-analysis technique based on combining results from several studies provides a different answer. Fouque et al used this technique to evaluate six clinical trials that included 890 nondiabetic, randomly assigned patients who were followed for at least one year [48]. They concluded that 5 of the 6 trials showed a reduction in the number of renal "deaths" (61 for low-protein diet groups versus 95 for control groups) and calculated an odds-ratio for renal death of 0.54 in patients prescribed a low-protein diet ($P < 0.002$), corresponding to a 46% decrease in the likelihood of kidney failure. Pedrini et al extended these results by including MDRD data: in nondiabetic patients, a low-protein diet was associated with a 33% reduction in the risk of renal failure or death ($P < 0.007$) and in diabetic patients, the diet reduced the risk of further kidney damage (a decrease in creatinine clearance or GFR or an increase in proteinuria) by 46% ($P < 0.001$) [49]. They also noted problems with the design of the MDRD Study and estimated that at least 1000 patients were needed to detect a 33% reduction in the risk of renal failure or death.

In principle, a low-protein diet could reduce the risk of renal failure either by slowing the progression of renal disease and by ameliorating uremic symptoms. Based on the secondary analyzes of the MDRD study showing that there is a strong correlation between actual protein intake and both the rate of GFR loss and dialysis entry, protection of residual renal function is likely to be one mechanism. The other factor is also important: attention to the diet can postpone the need for dialysis without compromising nutritional status [50]. In short, it seems likely that both mechanisms probably contribute to the beneficial effect of a low-protein diet.

ACKNOWLEDGMENTS

This work was supported in part by National Institute of Health grants DK40907 and DK37175.

Reprint requests to William E. Mitch, M.D., Renal Division, WMB 338, Emory University School of Medicine, 1639 Pierce Drive, Atlanta, GA. 30322 USA.
E-mail: wmitch@emory.edu

REFERENCES

1. Walser M, Mitch WE, Maroni BJ, Kopple JD: Should protein be restricted in predialysis patients? *Kidney Int* 55:771–777, 1999
2. Maroni BJ, Mitch WE: Role of nutrition in prevention of the progression of renal disease. *Ann Rev Nutr* 17:435–455, 1997
3. Chanutin A, Ludewig S: Experimental renal insufficiency produced by partial nephrectomy. V. Diets containing whole dried meat. *Arch Int Med* 58:60–80, 1936
4. Farr LE, Smadel JE: The effect of dietary protein on the course of nephrotoxic nephritis in rats. *Am J Pathol* 16:615–627, 1940
5. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 241:F85–F93, 1981
6. Daniels BS, Hostetter TH: Effects of dietary protein intake on vasoactive hormones. *Am J Physiol* 258:F1095–F1100, 1990
7. Rosenberg ME, Chmielewski D, Hostetter TH: Effect of dietary protein on rat renin and angiotensinogen expression. *J Clin Invest* 85:1144–1149, 1990
8. Remuzzi G, Ruggenenti P, Benigni A: Understanding the nature of renal disease progression. *Kidney Int* 51:2–15, 1997
9. The GISEN Group: Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 349:1857–1863, 1997
10. Kaysen GA. The nephrotic syndrome: nutritional consequences and dietary management, in *Handbook of Nutrition and the Kidney, 3rd Edn*, edited by Mitch WE, Klahr S. Philadelphia, Lippincott-Raven, 1998: pp. 201–212
11. Tapp DC, Wortham WG, Addison JF, Hammonds DN, Barnes JL, Venkatachalam MA: Food restriction retards body growth and prevents end-stage renal pathology in remnant kidneys of rats regardless of protein intake. *Lab Invest* 60:184–195, 1989
12. Bourgoignie JJ, Gavellas G, Sabnis SG, Antonovych TT: Effect of protein diets on the renal function of baboons (*Papio hamadryas*) with remnant kidneys: a 5-year follow-up. *Am J Kidney Dis* 23:199–204, 1994
13. Mitch WE, Buffington GA, Lemann J, Walser M: A simple method of estimating progression of chronic renal failure. *Lancet* 2:1326–1328, 1976
14. Mitch WE: Nutritional therapy and progression of chronic renal insufficiency, in *Handbook of Nutrition and the Kidney, 3rd Edn*, edited by Mitch WE, Klahr S. Philadelphia, Lippincott-Raven, 1998, pp. 237–252
15. Jones RH, Hayakawa H, MacKay JD, Parsons V, Watkins PF: The progression of diabetic nephropathy. *Lancet* 1:1105–1106, 1979
16. Ikizler TA, Greene JH, Wingard RL, Hakim RM, Parker RA: Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 6:1386–1391, 1995
17. Hakim RM, Lazarus JM: Initiation of dialysis. *J Am Soc Nephrol* 6:1319–1320, 1995
18. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of the death rate differences among facilities. *Am J Kidney Dis* 15:458–482, 1990
19. Kaysen GA: Biological basis of hypoalbuminemia in ESRD. *J Am Soc Nephrol* 9:2368–2376, 1998
20. Walser M: Does prolonged protein restriction preceding dialysis lead to protein malnutrition at the onset of dialysis? *Kidney Int* 44:1139–1144, 1993
21. Coresh J, Walser M, Hill S: Survival on dialysis among chronic renal failure patients treated with a supplemented low-protein diet before dialysis. *J Am Soc Nephrol* 6:1379–1385, 1995
22. Masud T, Young VR, Chapman T, Maroni BJ: Adaptive responses to very low protein diets: The first comparison of ketoacids to essential amino acids. *Kidney Int* 45:1182–1192, 1994
23. Tom K, Young VR, Chapman T, Masud T, Akpele L, Maroni BJ: Long-term adaptive responses to dietary protein restriction in chronic renal failure. *Am J Physiol* 268:E668–E677, 1995
24. Maroni BJ: Requirements for protein, calories, and fat in the predialysis patient, in *Handbook of Nutrition and the Kidney, 3rd Edn*, edited by Mitch WE, Klahr S. Philadelphia, Lippincott-Raven, 1998, pp. 144–165
25. Kopple JD, Coburn JW: Metabolic studies of low protein diets in uremia. *J Nitrogen Potassium Med* 52:583–594, 1973
26. Kopple JD, Levey AS, Greene T, Chumlea WC, Gassman J, Hollinger DL, Maroni BJ, Merrill D, Scherch LK, Shulman G, Wang SR, Zimmer GS: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease (MDRD) Study. *Kidney Int* 52:778–791, 1997
27. Goodship THJ, Mitch WE, Hoerr RA, Wagner DA, Steinman TI, Young VR: Adaptation to low-protein diets in renal failure: Leucine turnover and nitrogen balance. *J Am Soc Nephrol* 1:66–75, 1990
28. Maroni BJ, Steinman T, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 27:58–65, 1985

29. Maschio G, Oldrizzi L, Tessitore N, D'Angelo A, Valvo L, Lupo A, Loschiavo C, Fabris A, Gammaro L, Rugiu C, Panzetta G: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int* 22:371–376, 1982
30. Oldrizzi L, Rugiu C, Maschio G: The Verona experience on the effect of diet on progression of renal failure. *Kidney Int* 36:S103–S105, 1989
31. Rosman JB, Meijer S, Sluiter WJ, Ter Wee PM, Piers-Becht TP, Donker AJM: Prospective randomised trial of early dietary protein restriction in chronic renal failure. *Lancet* 2:1291–1295, 1984
32. Rosman JB, Langer K, Brandl M, Piers-Becht TPM, van der Hem GK, Ter Wee PM, Donker AJM: Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney Int* 36:S96–S102, 1989
33. Ihle BU, Becker GJ, Whitworth JA, Charlwood RA, Kincaid-Smith PS: The effect of protein restriction on the progression of renal insufficiency. *N Engl J Med* 321:1773–1777, 1989
34. Williams PS, Stevens ME, Fass G, Irons L, Bone JM: Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *Quart J Med* 81:837–855, 1991
35. Locatelli F, Alberti D, Graziani G, Buccianti G, Redaelli B, Giangrande A: Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. *Lancet* 337:1299–1304, 1991
36. Bergstrom J, Alvestrand A, Bucht H, Gutierrez A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-ups and better blood pressure control. *Clin Nephrol* 25:1–6, 1986
37. Walker JD, Dodds RA, Murrells TJ, Bending JJ, Mattock MB, Keen H, Viberti GC: Restriction of dietary protein and progression of renal failure in diabetic nephropathy. *Lancet* 2:1411–1414, 1989
38. Raal FJ, Kalk WJ, Lawson M, Esser JD, Buys R, Fourie L, Panz VR: Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: a 6-mo prospective study. *Am J Clin Nutr* 60:579–585, 1994
39. Zeller KR, Whittaker E, Sullivan L, Raskin P, Jacobson HR: Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 324:78–83, 1991
40. Barsotti G, Morelli E, Guiducci A: Three years' experience with a very low nitrogen diet supplemented with essential amino acids and keto-analogues in the treatment of chronic uremia. *Proc Eur Dial Transplant Assoc* 19:773–781, 1982
41. Mitch WE, Walser M, Steinman TL, Hill S, Zeger S, Tungsanga K: The effect of keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl J Med* 311:623–629, 1984
42. Walser M, Hill S, Ward L: Progression of chronic renal failure on substituting a ketoacid supplement for an amino acid supplement. *J Am Soc Nephrol* 2:1178–1185, 1992
43. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker LJ, Kusek JW, Striker G: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal failure. *N Engl J Med* 330:878–884, 1994
44. Teschan PE, Beck GJ, Dwyer JT, Greene T, Klahr S, Levey AS, Mitch WE, Snetselaar LG, Steinman T, Walser M: Effect of a ketoacid-aminoacid-supplemented very low protein diet on the progression of advanced renal disease: a reanalysis of the MDRD Feasibility Study. *Clin Nephrol* 50:273–283, 1998
45. Anonymous: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control Complications Trial. *N Engl J Med* 329:977–986, 1993
46. Levey AS, Adler S, Caggiula AW, England BK, Greene T, Hunsicker LG, Kusek JW, Rogers NL, Teschan PE, for the MDRD Study Group: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 27:652–663, 1996
47. Levey AS, Greene T, Beck GJ, Caggiula A, Kusek J, Hunsicker LG, Klahr S: Dietary protein restriction and the progression of chronic renal disease: What have all the results of the MDRD Study shown? *J Am Soc Nephrol* 10:2426–2439, 1999
48. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY: Controlled low protein diets in chronic renal insufficiency: meta-analysis. *Br Med J* 304:216–220, 1992
49. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 124:627–632, 1996
50. Walser M, Hill S: Can renal replacement be deferred by a supplemented very-low protein diet? *J Am Soc Nephrol* 10:110–116, 1999